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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RIGGINS, PATRICK S	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 11/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/729,861	CUI ET AL.	
	Examiner	Art Unit	
	Patrick S. Riggins	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 10-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 10-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 December 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/15/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Receipt of the Supplemental Preliminary Amendment filed 7/12/04 is acknowledged. In this amendment, claims 4, 6, 8, 10, and 11 were amended, claim 9 was canceled, and new claims 12 and 13 were added. Presently claims 1-8 and 10-13 are pending and under examination.

Information Disclosure Statement

2. The Information Disclosure Statement filed 7/15/04 has been considered and the signed and initialed Form 1449 is included with this Office Action. It is noted that since the Evers reference and the second Kőnig reference appear on two pages and as such it is unclear that the listing is for the same reference, these reference have been lined through. They have both been considered and to reflect this, they have been included on the attached PTO-892.

Drawings

3. Color photographs and color drawings are not accepted unless a petition filed under 37 CFR 1.84(a)(2) is granted. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and, unless already present, an amendment to include the following language as the first paragraph of the brief description of the drawings section of the specification:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings and black and white photographs have been satisfied. See 37 CFR 1.84(b)(2). The Brief Description of the Drawings for Fig. 2 on page 8 and Fig. 11 on page 11, both describe color figures yet no

color figures are present. Based upon the subject matter of these two figures, color images to appear to be a necessity in order to show the data that is presented in these figures.

4. The drawings are objected to because the images presented in Figures 2 and 11 are too dark to accurately depict the data that is presented. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

5. The disclosure is objected to because of the following informalities: Each of Figures 1, 2, 4-9, and 11 contain multiple panels. Each panel must be referred to in the brief Description. Thus, the Brief Description of the Drawings must be amended to comply with this requirement. As an example, "Fig. 1" on page 7, line 27 should be amended to read --Fig. 1A-1B--. The Brief

Description of Fig. 4 on page 8 refers to "ê", "s", "c", and "g", and the Brief Description of Fig. 7 on page 10 refers to "g" and "c". What do these symbols intend to represent? Further, the Brief Description of Fig. 5on page 9 refers to "B ® A" and "A® B" while from the figure it would appear that the "®" should instead be arrows.

Appropriate correction is required.

6. The amendment filed 12/5/03 as specification is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the last paragraph added to the end of page 30 seeks to incorporate all publications by reference. This is impermissible because the Disclosure of PCT/EP02/06175 contains no such statement, and this application is a continuation of that international application.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Objections

7. Claims 6 and 7 are objected to because of the following informalities: claim 6 recites "MDR" and "MRP" without first defining these terms in the claims. Though acronyms are permissible in the claims, they must be defined the first time they appear in the claims. Claim 7 is objected to because there is not agreement with respect to the format of the claim. BSEP is outside of the parenthesis, but MRP2 is within the parenthesis. Appropriate correction is required.

Claim Rejections - 35 USC § 112-2

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The recitation "the transport inhibitor" lacks proper antecedent basis. Claim 12 from which claim 10 depends is drawn to a method of identifying *whether* a candidate agent is a transport inhibitor. Thus, there is no assurance that claim 12 comprises a transport inhibitor, as the candidate agent may not be a transport inhibitor. It would be remedial to replace "the transport inhibitor" with --the candidate agent--.

10. Claims 10-13 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

11. The only method steps present in either of claims 12 or 13 are contacting the cell line with a candidate agent and "determining..." the effect. This insufficiently defines the method, as the method would only be functional if the cells of claim 1 were grown as a polarized monolayer, i.e. in a transwell format. Further there must be a step of contacting the cells with, for example BSP, in order to be able to track whether an agent is either substrate or an inhibitor. Finally, there must be some terminal step that establishes a link between any effect observed and the preamble of the claims.

Claim Rejections - 35 USC § 112-1

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-8 and 10-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for :

A double-transfected cell line transfected with,

a) a DNA sequence encoding an uptake transporter for organic anions operably linked with a promoter and

b) a DNA sequence encoding an export pump for organic anions or anionic conjugates operably linked to a promoter,

wherein the cell line is a polarized cell line that is either canine or human, the uptake transporter for organic anions is OAT1 (SLC22A6), OATP2 (SLC21A6), OATP8 (SLC21A8), or OATP-B (SLC21A9), and the export pump for organic anions or anionic conjugates is the bile salt export pump BSEP (ABCB11) or the multidrug resistance protein 2 MRP2 (ABCC2),

does not reasonably provide enablement for any non-polarized cell line transfected with any other DNA encoding an uptake transporter for organic anions or DNA encoding an export pump for organic anions or anionic conjugates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. To make and use the cell lines of the

invention in the fully claimed scope of the claims, the skilled artisan would be required to perform an undue level of experimentation.

14. A number of factors have been considered in making this assertion that undue experimentation is required to practice this invention as delineated by In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure

15. The claims comprise any cell line transfected with any DNA encoding a transporter for organic anions and any DNA encoding an export pump for organic anions or anionic conjugates. As the utility of the cell line is to determine whether agents inhibit vectorial transport, it is clear that only a polarized cell line would possess this utility and only a polarized cell line would be functional in this regard. The model depicted in Figure 3 and the description provided on page 15, section (E) of the specification. It is clear, that to measure transport of any substance across a cell monolayer, there must be distinct compartments, i.e. apical compartments and basolateral compartments. This allows the placement of the agent to be transported on either the apical or basolateral side of the monolayer, such that transport is measured by measuring the levels of the agent in the opposite compartment. This assay would not be functional if any non-polarized cell line were to be utilized in the invention. In this case, there would be no polarity with respect to the expression pattern of the transporters and as such there would be no differential compartments which could be utilized to ascertain transport. In other words any non-polarized

cell line transfected with an uptake transporter and an export pump, would take up the agent from the culture media and the export that agent directly back into that same culture media. Thus there would be no way to measure transport and thus any non-polarized cell line would lack any practical utility and for the purposes of the assay would be unusable.

16. The claims are further drawn to DNA sequences encoding any uptake transporter and any export pump. The specification only teaches OAT1, OATP2, OATP8, and OATP-B with respect to uptake transporters, and only MRP2 and BSEP for export pumps. While other pumps may be known in the art, there can be no assurance that any other pumps would function in the invention in order to detect substrates or inhibitors of the transporters. One might question why there would be this apparent differentiation. One need only look at the data presented in Figures 8A, 12, and 13 to see that different pumps can have vastly different activities and thus there can be no assurance that any pumps would be functional in the invention. Figure 8A shows that the combination of OATP8 and MRP2 can transport approximately 250-300 pmol/min/mg of protein, Figure 12 shows that OAT1 and MRP2 can transport approximately 30 pmol/min/mg of protein, while Figure 13 shows that OATP2 and MRP2 can only transport about 6 pmol/min/mg of protein. These vastly different capacities clearly show that different pumps have different activities, and absent some showing of functionality with different pumps, there is no assurance that other pumps would behave as desired.

17. This type of system for testing the effect of agents on vectorial transport appears to be novel and thus there is no art of record to support any further pumps than those described. The data presented in the invention, and discussed above clearly establishes that the combination of different pumps is unpredictable with regard to the activity that might be expected.

18. To identify pumps other than those disclosed or to utilize cell lines aside from polarized cell lines, the skilled artisan would be required to perform an undue level of experimentation. To identify further pumps or cell lines the skilled artisan would be forced to perform a high level of trial and error type experimentation, which clearly could not be considered routine. From the above analysis, it is clear that the specification as filed does not enable the skilled artisan to make use any cell line transfected with any DNA encoding an uptake transporter and any DNA encoding an export pump without undue experimentation.

19. Claims 1-8 and 10-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

20. As described above, the claims are broadly drawn to encompass any cell line transfected with any DNA encoding an uptake transporter for organic anions and any DNA encoding an export pump for organic anions or anionic conjugates. For uptake transporters, the specification teaches only of OAT1, OATP2, OATP8, and OATP-B. For export pumps, the specification teaches only of the bile salt export pump BSEP, and the multidrug resistance protein 2 MRP2. Aside from these specifically disclosed examples, there is no description regarding common structural features of either uptake transporters or export pumps. Indeed, the differences in the activities of the various pumps disclosed as described above clearly show that all uptake transporters do not share precisely similar functionality. The differences observed clearly show

that these species are not representative, as none of the disclosed examples is truly representative of the other examples. As none exemplifies the others, there is no way to expect that the disclosed species would be representative of the claimed genus.

21. Thus, absent a description of structure/function considerations, there is no evidence to suggest possession of the full genus of cell lines, uptake transporters, and export pumps. The differences in activity of the described pumps clearly establish that different pumps are not necessarily representative of the activities of each other. Further, as argued above, the apparent necessity of a polarized cell line, coupled with the exemplification in the specification only of polarized cell lines provides no evidence to the skilled artisan that the inventors were in possession of any non-polarized cell line double-transfected in the manner of the invention. From this, there is no evidence of record to suggest to the skilled artisan that the inventors were in possession of the full scope of the claimed invention at the time of filing.

Claim Rejections - 35 USC § 102

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23. Claims 1-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Chazot (J Biol Chem 269: 14403-24409 (1994), newly cited).

24. The claims are drawn to a double transfected cell line which contains both a DNA sequence encoding an uptake transporter, linked to a promoter, and a DNA sequence encoding an

export pump, linked to a promoter. The cell line can be a canine or a human or a kidney cell and the DNA sequences can be human. Both the uptake transporter and the export pump can be specific members of superfamily subgroups. Finally, the promoters to which the DNA sequences are linked can allow high expression.

25. Chazot discloses human embryonic kidney cells multiply transfected with different subunits of NMDA receptors (Abstract and whole document). As these cells are human, they necessarily contain each of the genes specified in claims 5 and 7, as each of these identified transporters and pumps are human. As the specification provides no definition for what is intended by "high expression", this term is open to broad interpretation. The endogenous promoter of each of the endogenous genes allows for expression of the genes in certain cell types. Thus, in these certain cell types, the genes are highly expressed relative to cells in which the promoters do not permit expression.

Conclusion

26. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick S. Riggins whose telephone number is (571) 272-6102. The examiner can normally be reached on M-F 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick Riggins, Ph.D.
Examiner
Art Unit 1633

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER